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THE EFFECT OF IV FENTANYL ON BIS VALUE AND RECALL

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ABSTRACT

Fentanyl is given as a premedication for surgery, as a supplement to regional and general anesthesia, as an analgesic for postoperative pain, and sometimes as an anesthetic. The purpose of this study was to describe the effect of IV fentanyl on BIS values and recall. Anesthesia providers often give fentanyl with a sedative to decrease anxiety, pain, ease induction and maintenance of anesthesia. The sedative properties of fentanyl may allow it to be given alone to accomplish the same goals.

The study consisted of a convenience sample of twenty adult patients undergoing elective surgery who consented to participate. Fentanyl was titrated to effect in increments of 25-50 mcg every two to five minutes up to a maximum (preoperative) dose of 5 mcg/kg. A picture was then shown and the patient assessed for recall after recovery from anesthesia.

The data analysis included descriptive statistics, computation of correlation coefficients, and regression analysis to examine the relationship between fentanyl and the dependent variables. Statistical significance was determined using two-sided tests and an alpha level of $p = 0.05$.

The coefficients of correlation between fentanyl and BIS values shows no statistically significant relationship: $r = -0.086$, $p = 0.72$

The question of legally obtaining informed consent from a patient after narcotic administration. Further research in this area may prove very valuable.

Key Words: **Bispectral index (BIS) values electrical encephalograph (EEG) sedation fentanyl patient recall**

SCHOLARLY PROJECT REPORT TITLE PAGE

THE EFFECT OF FENTANYL ON BISPECTRAL INDEX (BIS) VALUES AND RECALL

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Requirements for the
Degree of

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DECEMBER 2002

DEDICATION

To the most important people in our lives we dedicate the creation of this project. Without their love, encouragement, and support the attainment of a dream and the creation of this would not have been possible.

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CHAPTER ONE: INTRODUCTION

Anesthesia has three main components known as the anesthesia triad: hypnosis (loss of consciousness), adequate analgesia (determined by loss of reflex motor and autonomic response to surgical stimuli), and muscle relaxation.

Determining a patient's depth of anesthesia must take into consideration all three components. Subjectively assessing anesthetic depth is difficult for several reasons. The depth of anesthesia obtained using similar agents also varies considerably between patients.

Many variables (i.e. heart rate, blood pressure) currently used to determine need for additional anesthetic agents may be affected by factors completely unrelated to level of consciousness (LOC). For example, beta-blockers may mask a normal tachycardic response to pain or stress during surgery. Neuromuscular blockade and opioids, such as morphine or fentanyl, may inhibit somatic reflexes to painful stimuli yet the patient may be light with regards to their hypnotic state. Consequently, many patients are over-medicated and have delayed emergence from anesthesia, increased morbidity (i.e. nausea and vomiting) post-operatively, and prolonged recovery times (Kelley, 2001).

The Bispectral Index Monitor (BIS) uses processed electroencephalogram (EEG) parameters to assess the effect of anesthetics on the cerebral cortex. The BIS monitor was developed to give the anesthesia provider an objective level of anesthetic depth that helps to optimize anesthetic dosing.

Traditionally, anesthesia is induced and maintained by a variety of agents including volatile anesthetic gases, sedative/hypnotics, analgesics, and muscle relaxants. Extensive research has compared the effects of various combinations of these drugs and their effect on the BIS value during general anesthesia. Based on these studies, trends in the BIS value have been shown to be an accurate indicator of a patient's hypnotic state. These studies also show a direct relationship with BIS values and patient recall, with a BIS value of <70 having a low probability of recall (Glass et al., 1997, Kearse et al., 1998, Veselis et al., 1994).

The majority of research performed with the BIS monitor has involved the use of combinations of sedative-hypnotics, opioids, and volatile anesthetics mostly during general anesthesia. Research on the use of the BIS monitor during conscious sedation has just begun, and its usefulness in titrating sedatives safely is becoming more apparent. Opioids, specifically fentanyl, are sometimes used to provide conscious sedation because of their

sedative properties in addition to their analgesic properties. The effect of fentanyl alone on the BIS value, however, is unknown.

Background on Fentanyl

Fentanyl is an opioid that is primarily used for analgesia. Fentanyl, in high doses, has been shown to have an effect on the electroencephalogram (EEG) similar to sedative/hypnotics and volatile agents (Miller, 2000). Fentanyl was used as the principal anesthetic in cardiac surgery 10-20 years ago because of its safety in hemodynamically unstable patients. Fentanyl remains a major component of anesthetic care during cardiac surgery today. Currently, fentanyl is often used in lower doses to provide sedation and analgesia during diagnostic procedures (such as endoscopies), and in ventilator management of intensive care unit (ICU) patients. To date, research concerning the effect of fentanyl alone on the BIS value, and thus, level of sedation (hypnosis) and patient recall has not been conducted.

Purpose of the Study

The purpose of this study is to determine the effect of fentanyl on the BIS value, level of sedation, and subsequent patient recall after administration of fentanyl. Theoretically, since fentanyl has sedative properties, it should lower the BIS value. The ability to form memories (recall) should decrease as

well. The intent of this study is to describe opioid effect on BIS value and recall. If fentanyl has properties similar to standard sedative/hypnotics, the need to use multiple drug combinations to achieve sedation and analgesia may, theoretically, be reduced in some patients.

Research Questions

The following research questions guided the study:

1. What effect does fentanyl have on the BIS value in patients undergoing elective surgery?
2. What effect does fentanyl have on patient recall?
3. Is there a correlation between the BIS value and patient recall in patients receiving fentanyl?

Conceptual Framework

The BIS monitor gives a value that measures the effect of sedative/hypnotics and anesthetic agents on the hypnotic state of the brain. This value is based on an extensive database of thousands of EEGs and the correlating clinical and behavioral data collected from patients receiving many different variations of anesthetic agents. All of this information was processed and EEG descriptors were developed that correlated with clinical states; i.e. how awake or asleep the patient was compared to what their EEG showed at the time (Kissin, 2000). The descriptors were then ranked according to their ability to predict a particular clinical state of sedation. The BIS

monitor uses these descriptors to assign a BIS value to a patient that is indicative of that patient's depth of anesthesia (Kissin, 2000). The BIS value trends can thus be used as a guide for anesthetic dosing during surgery, potentially reducing over-dosage while minimizing the chance of awareness and recall.

Conceptual and Operational Definitions

BIS Value:

Conceptual- an objective level of sedation and hypnotic depth using the BIS monitor

Operational- an EEG-derived value that has been correlated with levels of sedation and anesthesia through research

Patient Recall:

Conceptual- a patient's recollection of events after administration of a known amnestic agent

Operational- a patient's ability to form explicit memories after administration of a known amnestic agent

Fentanyl:

Conceptual- an opioid with analgesic effects and some sedative properties

Operational- an opioid with known analgesic effects that has been shown to have effects on the EEG at higher doses indicative of an anesthetic state

Assumptions and Limitations

For this study, it was assumed that fentanyl has sedative properties and will consequently decrease the BIS value. The methodology of this study had several limitations. The study population consisted entirely of patients from one military medical center in the Midwestern United States. The population being studied excluded patients with dementia and patients under the age of 18. Recall was assessed using one picture for sake of convenience and to prevent delay of surgery.

Summary

The BIS monitor has been correlated through research as a predictor of a patient's level of hypnosis. Opioids have been used in conjunction with known amnestic agents so the effect of just opioids alone on the BIS value is unknown. If fentanyl has sedative and amnestic properties, they should manifest themselves by decreasing the BIS value and impairing recall. This could potentially reduce dosage requirements of opioids and sedatives, while maintaining adequate sedation and analgesia during procedures requiring conscious sedation. This could impact the nurse anesthesia profession by increasing understanding of the properties of fentanyl, reducing cost, side effects, and recovery time associated with use of multiple drugs.

CHAPTER TWO: LITERATURE REVIEW

Background

In 1847, John Snow described the various stages of ether anesthesia, and since then, scientists have tried to develop a method to determine level of consciousness (LOC) under anesthesia. Under-dosage of anesthetics is linked to instability in hemodynamics due to perception of pain and recall of intraoperative events, a major fear of a large percentage of surgical patients (Todd, 1999). The problem of intraoperative awareness increased with the addition of muscle relaxants, nitrous/narcotic and total intravenous anesthetic techniques to the anesthesia armamentarium (Rampil, 1999). The overall incidence of overt intraoperative recall varies from 0.2%-2% but the incidence of awareness during surgery is probably much higher (Kissin, 2000).

The anesthetic state has three components: unconsciousness (hypnosis), analgesia (loss of reflexive movement to noxious stimuli), and muscle relaxation. The peripheral nerve stimulator monitors the amount of muscle relaxation, while movement and autonomic responses to surgical stimuli provide feedback on the analgesic state. Until the advent of the BIS monitor, the primary way to estimate level of hypnosis was through changes in vital signs and the anesthesia provider's previous experiences. Many inconsistencies exist in evaluating a patient's hypnotic state in this manner.

Somatic reflex responses have been shown to occur at the spinal cord level and may be completely unrelated to the LOC in the cerebral cortex (Glass et al., 1997; Sebel et al., 1997). Perception of pain (analgesia) partly occurs at subcortical levels (i.e. limbic system) and is manifested by autonomic responses to noxious stimuli (Bower et al., 2000; Shapiro, 1999). Opioids decrease transmission of pain signals into the spinal cord, inhibiting normal withdrawal reflexes to painful stimuli. A patient receiving opioids may be aware despite lack of movement to a painful stimulus. Another patient may move in response to a painful stimulus because of a spinal cord reflex, yet is completely unconscious. Anesthetic agents block reception of pain signals at the level of the cerebral cortex. Spinal cord reflexes, however, remain intact.

Because the anesthetic state has several different components, determining a patient's hypnotic state without an objective tool is often unreliable. To confound the problem, anesthetic drugs may also affect one or more of these components differently. Some drugs, such as opioids and muscle relaxants, may give a false impression of the patient's LOC. Subjective tools have been used to estimate LOC, but their use often requires special training and their efficacy is questionable.

The BIS Monitor

Several techniques have historically been used to determine LOC, including heart rate variability, craniofacial electromyography, auditory and brainstem evoked responses, and EEG waveforms among others. Most anesthesia providers, however,

rely mainly on hemodynamic response (heart rate and blood pressure) to stimuli as their guide to administration of additional hypnotic agents, even though they are not a function of consciousness. None of these techniques have the sensitivity or specificity to allow a clinician to draw a conclusion about the patient's depth of anesthesia (Drummond & Weiskopf, 2000). The EEG, however, is an objective monitor of cerebral cortex activity and finding a way to use it efficiently to monitor the patient's hypnotic state has been the subject of intense research for several decades.

The EEG is used to assess the state of the higher centers of the central nervous system (CNS), mainly the cerebral cortex, by recording the electrical activity it produces. It has been known for many years that the EEG is sensitive to cerebral ischemia and hypoxia. More recently, anesthetic effects on the EEG have been described. Anesthetic agents directly suppress the cerebral cortex and some sub cortical structures causing unconsciousness (Rampil, 1998). Use of the EEG machine by anesthesia providers, however, is impractical for several reasons. EEG waveform printouts generate a huge amount of paper making it very difficult to observe trends. EEG tracings usually require a specially trained technician to interpret the waveforms.

Various ways of processing EEG signals have helped gain a better understanding of how consciousness is affected by a particular anesthetic drug within a narrow range. Defining an identifiable pattern to determine when a patient is conscious or

unconscious has been elusive. The EEG does not change in a predictable manner with anesthetic administration and similar anesthetic agents can cause very different EEG patterns. Another reason that EEG is difficult to use for assessing hypnosis is that most anesthesia providers use multiple classes of drugs for premedication, induction, and maintenance of anesthesia; all of which have significant but different EEG effects (Todd, 1998). The Bispectral Index Monitor (BIS) was developed to overcome the inherent problems associated with using the EEG alone in assessing LOC.

Development of the BIS monitor started with the collection of thousands of EEG recordings from a wide variety of patients undergoing many different anesthetic regimens. Clinical information (i.e. vital signs, anesthetic agent[s]) on each of these patients was also documented. The EEGs and clinical information were analyzed and ranked according to their ability to predict a specific clinical situation. From this information, constructs were developed that would best (statistically) correlate with a clinical condition. Based on these statistical constructs, the BIS monitor integrates several descriptors of the EEG into a single variable. This variable gives a value that is predictive of the level of hypnosis, while being relatively insensitive to a specific anesthetic or sedative agent. The statistically-based, empirically-derived combination of descriptors overcomes the limitations imposed by using the standard EEG monitor to determine LOC (Rampil, 1998; Todd, 1998).

The BIS monitor assigns a value from 0-100 that has been shown to have a high correlation with the LOC. A BIS score of 100 generally reflects the awake state, 80 reflects some sedation, 60 is moderate hypnosis/sedation, and 40 represents a deep hypnotic level; 40-60 is generally the range seen during general anesthesia (Kelley, 2001). The BIS monitor has been primarily used to monitor hypnosis during general anesthesia, but its use in intravenous (IV) conscious sedation has recently been investigated with promising results. BIS values in patients receiving IV sedation for various reasons have also compared to levels of sedation determined by using traditional subjective assessment tools.

IV Sedation

In a study using 25 subjects undergoing third molar extraction in an outpatient setting, the effects of IV sedation on BIS values were compared to subjective observations of patients' sedation level using the Observer's Assessment of Alertness and Sedation (OAA/S) tool. The OAA/S tool grades patients' sedation levels from 1= no response to tactile or verbal stimuli, to 5= awake. Patients were given standardized dosages of versed with fentanyl followed by propofol until an OAA/S score of 1-2 (responsive only to vigorous stimulation) was obtained; the BIS value was simultaneously recorded. OAA/S and BIS values were subsequently recorded every five minutes until full recovery. The results revealed a strong positive relationship between the BIS value and the OAA/S score ($p<.0001$; where $p<.05$ was considered significant). The researchers

concluded that the BIS monitor is an accurate, objective way of assessing depth of IV sedation using versed with fentanyl and propofol (Sandler, 2000).

Bower et al., (2000), studied the effects of IV sedation with valium and demerol during endoscopic outpatient procedures to determine if there was a correlation between OAA/S and the BIS value. The endoscopist was blinded to the BIS value and administered additional sedation or analgesia to the patient based on their assessment of the patient's need for redosing. The results showed a significant correlation between BIS and OAA/S scores ($r=0.6$, $p<.00001$; $p<.05$ was considered significant). BIS and OAA/S scores corresponded to the patient's need for additional sedation as determined by the endoscopist (who was blinded to both the BIS and OAA/S). A serendipitous finding of this study showed that the deeper the sedation (according to OAA/S), the more variable the corresponding BIS level between patients. An OAA/S score of 2 correlated with a mean BIS value of 70 and had a standard deviation of 16. An OAA/S score of 5 had a

corresponding mean BIS value of 97 and a standard deviation of 1.3. The authors attribute this disparity to increasing difficulty in accurately assessing deeper levels of sedation using a subjective tool and comparing it to an objective BIS value (Bower, et al., 2000). The previous study did not indicate this disparity in their findings.

A third study used the BIS monitor to predict the depth of versed-induced sedation according to the level determined by the

OAA/S tool. Twenty-six healthy adults were given 0.5-1.0 mg incremental doses of versed every 6-10 minutes using the OAA/S to determine the sedation level with the goal of an OAA/S score of 2 with the BIS value continuously recorded. Data were collected during loss and return of consciousness. Results showed that the BIS value correlated the most with OAA/S during onset of sedation (Spearman's Rho= 0.8) and recovery (Spearman's Rho= 0.6). With increasing sedation, there was a progressive decline in the BIS value and with recovery, the BIS value increased. The researchers conclude that BIS values can accurately predict the depth of versed-induced sedation (Liu, Singh, & White, 1996).

IV sedation is also used in intensive care units (ICU); the degree of analgesia and amnesia requirements for ICU patients, however, has not been standardized (Bloom, 1997). Great disparity exists among intensive-care providers as to how much and which kind of sedatives their patients should receive. This, among many other factors, has made assessing the sedation level of critically-ill patients in ICUs extremely difficult.

Simmons, Riker, Prato, and Fraser (1999) evaluated sedation/analgesia in 63 adult ICU patients requiring mechanical ventilation using the BIS monitor and the Sedation-Agitation Score (SAS). Use of the SAS tool involves stimulating a patient and evaluating their response to that stimulus. Investigators recorded the SAS throughout the entire data collection period and were blinded to the BIS values. A baseline BIS value was determined after 15 minutes without stimulation and every 15

minutes thereafter regardless of the level of stimulation to get an average BIS value.

A separate investigator reviewed the tracings to determine the average BIS value several days after the initial recording. Ventilator settings and medications were recorded. Heavily sedated patients with a SAS score of 1-2 (n=20) compared to patients with a SAS score of 3-5 (n=44) had more severe lung disease with higher ventilatory requirements and lower baseline BIS values (66 vs. 78). Patients requiring neuromuscular blockade (n=4) had the lowest average SAS score (1.5); they did not, however, have a lower average BIS value compared to the other groups (possibly because of inadequate sedation). The researchers attribute this discrepancy to the extremely small number of patients requiring neuromuscular blockade in this study. A trend towards heavier sedation for sicker patients became apparent in this study. Even though sedation was not standardized and the SAS and BIS were reviewed separately, the researchers conclude there is a strong correlation between the BIS value and SAS score despite the limitations of their study.

Monitoring the hypnotic state in ICU patients is difficult. Subjective clinical assessment of sedation varies according to the sedation scoring system used and the individual using the tool. Once patients are deeply sedated, the validity of subjective scoring systems of sedation decreases. If a patient is receiving neuromuscular blockade, it is impossible to accurately assess sedation levels using these tools. Many patients have a BIS value less than 60 possibly indicating over-

sedation and unnecessary cost (De Deyne, 1998). Preliminary findings indicate the BIS monitor may be useful in assessing sedation levels in ICU patients despite subjective components, limited sample sizes, and the large number of variables (Shapiro, 1999).

Generalizations about the usefulness of the BIS monitor in evaluating LOC during IV sedation can be made from the research results. The ability of the BIS to predict loss of consciousness during sedation has been consistently demonstrated in these studies using a variety of drug combinations in a variety of situations. The usefulness of the BIS monitor in this capacity becomes apparent. Sedation, however, does not automatically guarantee impairment of memory formation.

Recall

Although BIS values are useful in assessing sedation levels, the usefulness of the BIS monitor in establishing values that would define a threshold for memory formation (recall) is undetermined. Recall occurs when a person forms a memory despite the presence of therapeutic doses of sedative/hypnotic agents (Miller, 2000). Evaluating recall is not straightforward. In many instances, patients who respond appropriately to verbal commands under the influence of a sedative/hypnotic agent, have no recall of the event. This indicates that the relationship between following commands and memory formation is not direct.

The likelihood that a patient will have recall depends on the strength of the stimulus and the sensory threshold at the

time the patient experiences the stimulus (Hilgenberg, 1981). Recall during anesthesia has been associated with more potent stimuli such as laryngoscopy, intubation, skin incision, sternotomy, and aortic root dissection (Kissin, 2000). Researchers have attempted to define a range of BIS values in which memory formation would be impaired in all patients with variable results.

Flashion, Windsor, Sigl, and Sebel (1997) evaluated 40 surgical patients and induced anesthesia using either thiopental or propofol followed by a neuromuscular blocking (NMB) agent. Before induction, a tourniquet was applied to the dominant arm and inflated above the systolic blood pressure to prevent any NMB agent from reaching the arm. This allowed preservation of the ability to move the hand after the onset of the NMB agent to determine return of consciousness. The patient was prompted to squeeze the investigator's hand every 30 seconds after induction. The BIS value was followed throughout this time period until the patient responded to the command; anesthesia was then reinduced. The propofol group had higher BIS values than the thiopental group (62 vs. 43) and longer intervals of unconsciousness (529 sec. vs. 421 sec.) showing a large disparity between both drugs. This made it statistically difficult to establish an across-the-board threshold BIS value for loss of consciousness. During this study, no patient was responsive with a BIS value less than 58. Most significantly, no patient experienced recall of events despite responding to commands, reinforcing the statement that responses to commands

and recall do not have a direct association.

Other studies indicate patients may respond to commands and have recall with very low BIS values. Glass et al., (1997) correlated BIS value with response to verbal commands in 72 healthy volunteers who received incremental doses of propofol, midazolam, or isoflurane to reach physiologic target serum concentrations. The lowest recorded BIS value, in which a patient responded to command, was 40, although 95% of patients were unconscious (unresponsive to commands) with a BIS value of 50. Lubke, Kerssens, Phaf, and Sebel (1999) found evidence of memory formation in trauma patients with BIS values between 40-60 who were anesthetized with isoflurane and fentanyl. Similarly, another study in which BIS-monitored patients received propofol with a regional anesthetic had a patient respond to command with a BIS value of 40 (Gajraj, Doi, Mantzaridis, & Kenny, 1999). These studies indicate that responsiveness, and perhaps recall, can occur with BIS values as low as 40. This does not mean that every patient should be kept at such a low BIS prophylactically. The anesthesia required to reach a BIS of 40 may be too deep for most patients, increasing the chances of undesired hemodynamic effects and prolonged emergence from the anesthesia (Drummond & Weiskopf, 2000).

Liu, Singh, and White (1996), studied recall of ten patients undergoing surgery with a regional anesthetic who were given propofol for sedation. The patients were shown a picture and then received 40 mg of propofol IV. They subsequently received incremental doses of propofol every 5-10 minutes and the depth

of sedation was assessed using the OAA/S tool. BIS values were recorded continuously during the entire procedure. Upon achieving OAA/S scores of 4, 3, 2 and 1 respectively, patients were shown a different picture and the same process was repeated as the patient recovered from the sedation. Picture recall was tested in the recovery room. Patient recall of the pictures decreased with increasing depth of sedation and decreasing BIS value (OAA/S 5, BIS 94, %recall 100%; OAA/S 1, BIS 76, %recall 0%). The researchers recommend a BIS value of 80 to prevent recall during propofol-induced sedation.

In this study, a BIS value of 87 was associated with 40% recall, whereas a BIS value of 80 had 0% recall despite such a small difference in the BIS value. Based on these studies, it is evident that the BIS value in which recall occurs varies between patients and type of anesthetic used. Failure to recall a picture during a regional anesthetic, however, does not mean a patient would not recall more noxious (painful) stimuli with similar BIS values.

Comparable BIS values achieved using different agents do not necessarily represent the same level of sedation (Drummond and Weiskopf, 2000). A BIS value that predicts consciousness in one patient may not predict it in another patient. BIS monitoring is best used to tailor each individual patient's anesthetic profile; a therapeutic window of 50-60, however, is generally accepted to predict unconsciousness and impairment of memory formation and thus, absence of recall (Miller, 2000).

The use of the BIS monitor in assessing LOC during general

anesthesia is well documented. The use of the BIS monitor during conscious sedation using propofol, midazolam and other IV hypnotic/sedative agents has been the subject of more recent research. Opioids, such as morphine and fentanyl, are occasionally used as sedatives. Research conflicts, however, concerning their primary use as sedatives. No research has been done to describe the effect that opioids have alone on the BIS value.

Fentanyl

Fentanyl is the preferred opioid used by anesthetists and is used extensively. Fentanyl is given as a premedication for surgery, as a supplement to regional and general anesthesia, as an analgesic for postoperative pain, and sometimes as an anesthetic. Small doses of fentanyl (200 mcg) produce minimal EEG changes, whereas higher doses (30-70 mcg/kg) result in high-voltage slow (delta) waves, suggesting an anesthetic state. Fentanyl has been used as the principal anesthetic in cardiac surgery because of its stable hemodynamic profile. High-opioid anesthetic techniques, however, have been associated with higher incidences of recall. Since high-opioid anesthetic techniques have been correlated with an increased incidence of recall and awareness, it is often taken as evidence that opioids produce poor amnesia and should not be used in this capacity (Veselis et al. 1994).

Studies indicate that fentanyl has poor sedative and amnestic properties despite its occasional use as such. Tomiei, Ikeda, and Morita, 1998 state that fentanyl alone, even at high

plasma concentrations, is a poor sedative agent and should be combined with a known sedative/hypnotic agent such as propofol. One study compared the amnestic effects of equisedative concentrations of midazolam, propofol, thiopental, and fentanyl. Equisedative dosing was determined by establishing the Cp50 (50% loss of memory for words) for each drug and normalizing the drug concentrations using logisitic regression to equisedative effects as compared to midazolam. Sixty-seven patients were randomized equally and received one of the drugs listed. The fentanyl group received ondanestron as well, to offset nausea (n=11); a placebo group received ondansetron only (n=11). Participants were given standardized memory tests at different intervals during the study. The authors indicate from their results that fentanyl has little effect on memory. They offset this statement in two ways. The first is that ondanestron stimulates the serotonergic system, which plays a role in memory function. Ondanestron could have enhanced the memory function of the participants receiving fentanyl. The second is that many of the participants receiving fentanyl still had nausea, despite ondansetron, which could have increased their arousal state and improved their memory performance (Veselis, Reinsel, Feshchenko, & Wronski, 1997).

Despite these findings, fentanyl is still used as a sedative for ventilator management in ICU patients and during minor surgical and diagnostic procedures (Miller, 2000, Veselis et al. 1994). The sedative properties of fentanyl are clinically accepted, but only one study found specifically studied

fentanyl's effect on memory formation.

In a study including nine healthy, non-surgical participants, low plasma concentrations of fentanyl and its effect on memory and behavioral performance were studied. Participants were randomized to two groups, one group received fentanyl (n=6) and the other received placebo (n=3). Fentanyl was administered until three target plasma concentrations were achieved (1.0, 1.5, 2.5 ng/ml). Several different memory and psychomotor tests were administered starting at baseline, when target concentrations were reached, and during recovery. Researchers assessed recall of the participants by showing them pictures before the infusion began and then showing them again after recovery. Researchers had to prompt the participants who received fentanyl, and even then, recall was incomplete. A visual analog scale was also used to assess mental and physical sedation at maximum concentration. Fentanyl subjects were significantly more sedated than the placebo subjects ($p<0.0001$). The results indicated that fentanyl produced a progressive decline in memory function and recall ($p<0.02$) as well as a decrease in psychomotor function of 15-30% (Veselis et al. 1994).

The fentanyl doses these participants received are similar to what patients receive for pain control as well as sedation. The results of this study indicate that even low doses of fentanyl can have a distinct impact on memory formation. The amnestic effects produced by fentanyl are not as dense as the effects seen with benzodiazepines because these participants

were still able to recall some of the pictures incompletely with prompting. This property could possibly account for the higher incidence of recall when used as a primary anesthetic (Veselis et al. 1994).

The studies previously mentioned have indicated that fentanyl is a poor sedative and lacks amnestic qualities. One study was inconclusive about the true effects of fentanyl on memory because of other variables, i.e. presence of nausea and other memory-stimulating drugs given concurrently (Veselis, Reinsel, Feshchenko, & Wronski, 1997). The only study reviewed that indicated fentanyl has distinct effects on memory had only six participants (Veselis et al. 1994). The effect of fentanyl, and opioids in general, on memory formation and recall is ambiguous and conflicting in the literature. With the invention of the BIS monitor, the sedative effects of fentanyl can be quantified and compared to other known sedative/hypnotic agents. To date, no research has been done with an opioid alone to assess the level of sedation achieved and its effect on recall, using the BIS monitor.

Summary and Conclusions

The BIS monitor measures the effects of sedatives and anesthetic agents on the hypnotic state of the cerebral cortex. Monitoring the level of hypnosis can be beneficial to the patient by decreasing the risk of intraoperative awareness while optimizing administration of hypnotic agents intraoperatively. The BIS monitor has been shown to have a positive correlation with the hypnotic state of the patient using standard sedative

and anesthetic agents (Do et al. 1999). The BIS trends, however, are the best way to use the BIS in assessing a patient's level of sedation. Considerable variation exists between BIS values and corresponding LOC among patients. For example, a BIS value of 70 may mean deep hypnosis for one patient and moderate sedation with high recall probability for another.

There is a gap in the literature with regards to the use of fentanyl as a primary sedative and its effect on the BIS value and recall. The purpose of this study was to describe the effect fentanyl has on the BIS value and recall. Fentanyl has traditionally been given in conjunction with other sedatives as the analgesic component. The use of multiple drugs to achieve adequate sedation and analgesia could potentially increase recovery time. Since fentanyl has sedative and analgesic properties, it may be possible to reduce the use of additional sedatives. This could potentially decrease recovery time and drug costs, as well as decrease the potential for adverse side effects associated with using multiple sedatives.

CHAPTER THREE: METHODOLOGY

Research Design

The purpose of this study was to determine the effect of IV fentanyl on the BIS value and patient recall. This study used a physiologic, descriptive design. Participants included in the study consisted of patients undergoing elective surgery at a military medical treatment center in the Midwestern United States.

The primary researchers and anesthesia providers who were trained in the study protocols collected the data. BIS monitoring is used during most anesthetics at this medical treatment center. Most anesthesia providers in this institution administer fentanyl routinely in the preoperative holding area, before induction of anesthesia, and during surgery. Only the fentanyl administered preoperatively in the holding area was considered in this study.

Data collection began in the holding area as patients proceeded through normal activities in this area which included: the anesthesia interview and assessment, verification of paperwork completion, IV insertion and starting maintenance fluids. Monitoring during fentanyl administration followed established guidelines set in the Anesthesia Element Instruction 44-02 (see attached). Pulse oximetry was monitored on all

study participants. Oxygen and emergency equipment were immediately available. The BIS monitor lead was then attached to the patient's forehead in accordance with manufacturer's recommendations. The BIS monitor was interfaced with a laptop computer for continuous recording of BIS values.

Fentanyl was titrated to effect by the researchers at a rate of 25-50 mcg every two to five minutes up to a maximum (preoperative) dose of 5 mcg/kg. Total dose given varied widely according to patient response and anesthesia provider preference. Once the fentanyl titration was completed, the patient was shown a single picture as an indication of recall postoperatively. The BIS lead remained in place for intraoperative monitoring at the discretion of the anesthesia provider. The entire data collection period lasted approximately 10 minutes.

Participants were recovered per standard department protocol. The participants met standard Post Anesthesia Care Unit (PACU) discharge criteria before evaluation of recall took place. Some participants' evaluation of recall took place in the Same Day Surgery Unit or the inpatient unit where the patient was transferred after being discharged from the PACU; all evaluation of recall took place within 24 hours of discharge from the PACU.

Sampling and Setting

The research participants consisted of a convenience sample of patients undergoing elective surgical procedures at a military medical treatment center in the Midwestern United States who consented to participate in this study. Exclusion criteria included: age under 18, known allergy to fentanyl, dementia, pregnancy, patient refusal, and any patient the anesthesia provider felt that giving pre-operative fentanyl to in the holding area would be inappropriate. The researchers were not blinded to the fentanyl dosage given, since it was considered necessary for the anesthesia provider to know how much fentanyl a patient had received.

Because fentanyl was expected only to cause a moderate effect in the BIS value, a sample size of 75 was initially projected using a two-tailed test and an alpha level of .05 which would give a power of .80. Application for Internal Review Board (IRB) approval was applied for in July 2001 and final approval was obtained in January 2002.

Instructions from the IRB included: initial enrollment of ten participants with internal anesthesia department review by the Chief Anesthesiologist and, with approval, enrollment of an additional 15 patients. After data were collected on 25 patients, the study results were to be presented to the IRB to determine if further enrollment was warranted.

In accordance with IRB instructions, the Chief Anesthesiologist reviewed the results of the first 10 participants and approval was obtained to continue. An additional 10 participants were enrolled for a total sample size of 20 participants. Further enrollment was not attempted due to time constraints and because it was felt that increasing the sample size would most likely not add much statistical significance.

Measurement Methods

The BIS monitor is commonly used during general anesthesia for monitoring patients' level of hypnosis according to trends in their BIS values. BIS values and the corresponding levels of sedation may vary between patients and medications used which makes generalizations of BIS value ranges more difficult. Several studies have indicated that the BIS value, however, is a valid and reliable indicator of depth of hypnosis and level of sedation when BIS value trends are used in an individual patient (Bower et al, 2000; Liu, Singh, & White, 1996).

The BIS monitor was interfaced with a laptop computer and BIS values were automatically recorded every five seconds for each participant. Participants' demographics, including: weight, total fentanyl dose, type of anesthetic (regional, monitored anesthesia care [MAC], general), and picture recall, were recorded in SPSS.

Protection of Human Rights

Patients were informed of the study during their preoperative interview the day of surgery; patients who agreed to participate were consented at this time. All eligible patients who were informed of the study agreed to participate. Risks were explained in the consent form and the researchers answered any questions.

The patients were not exposed to any additional risk by participating in this study. The risks of this study were inclusive with the risks of IV therapy and medication administration required for surgery. The possible risks specifically associated with this study included: potential, for allergic reaction to include anaphylaxis from IV administration of fentanyl, irritation from the IV catheter (phlebitis), blood collection under the skin as a result of venous cannulation (hematoma), infection at the IV site, over-sedation with respiratory depression, nausea/vomiting, and pruritis. All of these complications were related to anesthetic administration in most surgeries. Participants were free to withdraw from the study at any point without consequence and still receive preoperative sedation if appropriate.

Confidentiality of the participants

Assigning a subject number protected confidentiality of each of the participants. All demographic data had no associated

name or social security number. All data were saved on floppy disk and remained in the sole possession of the researchers during this study. No participant identifying information was stored on the disks. The military medical center's research department, in accordance with institution policy, stored the disks and consent forms securely. One copy of the consent form was given to each participant and one copy was filed in each participant's medical record.

CHAPTER FOUR: STUDY FINDINGS

Introduction

The research questions identified in Chapter One included: 1. What effect does fentanyl have on the BIS values in patients undergoing elective surgery? 2. What effect does fentanyl have on patient recall? 3. Is there a correlation between the BIS value and patient recall in patients receiving fentanyl? The findings of this study revealed that although patients receiving fentanyl may have BIS values consistent with deep sedation (BIS value <70) and amnesia according to the manufacturer, the patient's ability for explicit gross recall was not affected in this study.

Total fentanyl dosage varied considerably between the participants in this study. All participants stated that they "felt very relaxed" after administration of fentanyl, and at points, appeared to be sedated according to their BIS value and/or generalized appearance. All participants were shown the predetermined picture before they were taken back to the operating room and recall was assessed when recovery from anesthesia criteria were met. All participants had complete recall of the picture shown before surgery.

Based on these findings, the dosage range of fentanyl used in this study had no significant effect on (lowest) BIS value ($r=-0.086$), and no effect on ability to form memory (recall). A

BIS value less than 70 should cause a deep hypnotic state in general. A small number of participants receiving fentanyl in this study achieved BIS values in this range. These participants appeared sedated but, when lightly stimulated, were able to respond quickly and appropriately to command, maintained their own airway, and had complete awareness; BIS values after stimulation in all participants increased to greater than 90 no matter how low the BIS value before stimulation.

The use of fentanyl in low doses as a sedative/amnestic agent has not been studied a great deal. Based on the fact that the participants in this study remained in a relatively high state of consciousness after receiving fentanyl, reinforces the findings of Tomiei, Ikeda, and Morita (1998) who compared fentanyl with other sedative/hypnotic agents and concluded that fentanyl had poor amnestic and sedative properties. In contrast to the findings of this study, a study by Veselis et al. (1994) included nine healthy volunteers who were given fentanyl and subsequently given more complex memory tests concluded that fentanyl did affect memory function and recall. The memory test used in this study only evaluated gross recall; subtle changes in memory function may have existed but would not have been detectable using only one basic picture to evaluate recall. In order to truly rate the ability of fentanyl to sedate (objectively), sedation must first be put into context.

The sedative properties of fentanyl can be rated as either excellent or poor depending on the desired outcome. If low-dose fentanyl is solely being used to cause hypnosis and amnesia, the outcome may be less than satisfactory. If the outcome desired is a comfortable, relatively alert patient who can maintain their own airway and amnesia is not required, the sedative properties of fentanyl can be rated as excellent.

Data Analysis

All data was entered into SPSS for analysis. The data analysis was guided by the three research questions as stated in Chapter I of this proposal. The questions focused the analysis of the data on the relationship of fentanyl to the BIS values of patients undergoing elective surgery and to their recall of the picture shown preoperatively after recovery from anesthesia. The relationship between BIS values and total fentanyl dose was analyzed by computing Pearson's correlation coefficient (r value) with significance determined by an alpha level (p value) of 0.05 or less.

The correlation coefficient revealed an r value of -0.086 with p= 0.72. These values reveal that there is no statistically significant relationship between BIS values and total fentanyl dosage given. Analysis of the relationship between BIS values and recall was not performed since all participants had 100% recall in this study.

Limitations of the Study

The results of this study indicate that: fentanyl does cause objective (appearance of sedation) and subjective (participants stating that they feel "relaxed") sedation yet has no significant effect on BIS values and no effect on gross simple recall. The study, however, had several limiting factors that could have influenced the results.

In order to improve the power of the study, a larger sample size of 75 was originally projected but was reduced due to time constraints. Although a larger sample size could have identified trends based on demographics that this study may have missed, it was felt that additional enrollment would most likely not have lead to statistically significant results.

Every attempt was made to collect data for this study in a realistic environment; the preoperative holding area. There was a considerable amount of stimulation for the study participants because of the noisy holding area, including interruption by physicians, conversation between providers and patients in adjacent areas and equipment alarms (i.e. IV pumps). Participants, at times, were "awoken" by these events causing an immediate increase in their BIS, and/or preventing a decrease in the BIS value that may have occurred.

The researchers administering the fentanyl were not blinded to the dose they were giving or to the BIS value and this could

have influenced total dosage given. It was considered necessary for the anesthesia provider who would assume care of the participant to know how much fentanyl he or she had received.

Although this study used the BIS monitor as an indicator of sedation/level of hypnosis, several participants had BIS values less than 80 but were very alert whereas other participants appeared sedated but had BIS values greater than 95. An objective observer sedation tool scored by a second researcher blinded to the BIS could have identified significant levels of sedation. All participants indicated that they "felt very relaxed", a subjective tool of sedation or relaxation, in retrospect, would have been valuable.

The picture used to evaluate recall was shown at the end of fentanyl administration and not when the lowest BIS value was achieved. Only one picture was shown that could be easily identifiable for the participants, no time was allotted for more complex memory tests to be administered which may have shown more subtle effects on memory function.

Observations

Fentanyl is also frequently used by anesthesia providers to blunt the effects of laryngoscopy such as increased heart rate and blood pressure. Several anesthesia providers who assumed care of the study participants after they received fentanyl commented that the study patients seemed to have had a smoother

induction (less increases in heart rate and blood pressure). The study participants did receive fentanyl perhaps a few minutes earlier than other patients usually do which could account for this effect. Recording of vital signs before, during, and after induction was not part of the study design due to time factors.

As dosage of fentanyl increased, so did the incidence of pruritis which was not bothersome to the participants. Three participants complained of nausea after fentanyl administration (one of these participants became nauseated while standing to void) and were treated with ondansetron in an appropriate dose.

CHAPTER FIVE: CONCLUSIONS

The purpose of this study was to determine the effect of fentanyl on BIS value and patient recall. Previously, studying the effects of low dose fentanyl as a sedative agent and its effect on the BIS had not been done. This study used a physiologic descriptive design with a convenience sample of 20 participants. Fentanyl, in low to moderate dosage, caused no significant decrease in the BIS value and had no effect on participant recall in this study.

Recommendations for Further Study

This study had many limiting factors that could have significantly influenced the results. Recommendations for further study should answer these questions:

1. Does low to moderate dosage of fentanyl cause different levels of sedation or impairment of recall based on age, gender, or weight?
2. Does administration of fentanyl in a controlled environment cause a different level of objective sedation than in a more realistic environment such as the preoperative holding area?
3. Does use of an objective sedation tool by a second researcher such as the OAA/S tool correlate with BIS values?
4. Does the total fentanyl dosage given change if the researchers are blinded to the BIS value?
5. Does the total fentanyl dosage given change if the

researchers are blinded to the amount of fentanyl they are administering for sedation?

6. Would use of more sophisticated memory tests during and after administration of fentanyl determine if there is an effect on more complex memory formation?

The results of this study did not show statistical significance yet several valuable findings were noted during data collection.

All patients "sedated" with fentanyl remained easily arousable, responded appropriately and had complete basic recall even with higher doses. Use of other sedative agents may sometimes cause a patient to become dysphoric and uncooperative unless they are given additional sedatives to "deepen" them. This can cause problems in itself; patients receiving strictly narcotics in this study did not experience this effect. A cooperative patient is always a benefit. Another benefit of a patient strictly receiving narcotics is their ability to recall facts and remain relatively alert.

The question of legally obtaining informed consent from a patient after narcotic administration because of its supposed effect on cognitive function may be called into question based on the data from this study. Further research in this area may prove very valuable since many procedures are put off because a patient cannot legally give informed consent while receiving

narcotics.

The results of this study did not show statistical significance, but they were clinically significant and can be useful to the anesthesia profession. The power of fentanyl to control pain is well known; its usefulness for sedation as a stand-alone agent was very apparent in this study and deserves further study.

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Appendix 1

Memorandum of IRB APPROVAL:

- **UNIFORMED SERVICES UNIVERSITY**
- **WRIGHT-PATTERSON AIR FORCE BASE**

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

January 23, 2002

MEMORANDUM FOR CAPTAIN MARY JO BURLEIGH, CAPTAIN RONALD WYATT, AND CAPTAIN TONY BANKS, GRADUATE SCHOOL OF NURSING

SUBJECT: IRB Approval for Protocol **T061CY** Involving Human Subject Use

Your protocol entitled ***"The Effect of IV Fentanyl on the Bispectral Index (BIS) Value and Recall"*** received an expedited review and was **APPROVED** by Edmund G. Howe, M.D., J.D., Chairperson, Institutional Review Board on 1/23/2002. This protocol is considered to be not greater than minimal risk in accordance with 32 CFR 110 (b)(1) Suppl. F(7), and this approval will be reported to the full IRB scheduled to meet on 2/14/02. *Please note that while this approval letter allows you to begin your study, the IRB can, at its meeting in November, decide to hold the study in abeyance if it feels that additional information is needed.*

The IRB understands that the purpose of this study is to determine the effect of fentanyl on the BIS value, level of sedation, and subsequent patient recall after administration of fentanyl. Participants in the study will be undergoing elective surgery at a military medical treatment facility. Fentanyl is normally given in the preoperative holding area at the facility. The BIS monitor is commonly used during anesthesia for monitoring a patient's level of hypnosis. The study protocol has participants look at a picture once the BIS level shows an effect. Later the participants will be asked if they remember the picture when they are in the recovery room. This study was approved by the Wright Patterson Air Force Base Medical Center IRB on 17 October 2001 (Major William Craig, WPAFB Medical Center PI).

Please notify this office of any amendments you wish to propose and of any adverse events which may occur in the conduct of this project. If you have any questions regarding human volunteers, please call me at 301-295-3303.

Kathryn H. Knudson

Kathryn H. Knudson, Ph.D.
LTC, MS, USA
Human Research Protections Program
Administrator and Executive Secretary, IRB

cc: Director, Research Administration

DEPARTMENT OF THE AIR FORCE
74TH MEDICAL GROUP
WRIGHT-PATTERSON AIR FORCE BASE, OHIO

17 October 2001

MEMORANDUM FOR 74 MDOS/SGOSA
ATTN: CAPT WILLIAM CRAIG

FROM: 74th MDOS/SGOA
4881 Sugar Maple Drive
WPAFB OH 45433-5529

SUBJECT: Notification of Protocol Approval

1. Your protocol, "What is the Effect of Fentanyl on BIS Values and Recall?," has been approved by the WPMC IRB. The Surgeon General's Research Oversight Committee (SGROC) has also reviewed and approved this protocol. This protocol has been assigned tracking #FWP20010043H.

2. Let me know how many informed consent document (ICD) packages you will need to start your study. When you receive your ICD packages, you may begin entering patients. Proper documentation of the informed consent process is critical and cannot be over emphasized. Each ICD package will include a set of three original consent forms with the "final destination" stamped on the bottom of the first page. It is mandatory that the Clinical Investigations office receive the Clinical Investigations File Copy promptly after it is executed. An unsigned copy should be given to the patient for his/her information. Finally, a copy is to be placed in the patient's medical record along with a notation that he/she has been entered into an investigational protocol. If the protocol involves an outpatient procedure, the consent form should be placed in the outpatient record. If it involves an inpatient procedure, the consent form should be placed in the inpatient record but both records should be annotated that the patient is on the study. This notation insures that other physicians treating the patient are aware of the protocol.

3. All amendments made to your protocol must be submitted to Clinical Investigations for approval prior to implementation.

4. Progress reports will be due annually. The first one will be due in July 2002. You will receive a reminder 30 days in advance when your report is due. When progress reports are submitted, Clinical Investigations will conduct a random patient record audit to insure that the consent form is present in the record, progress notes indicate the patient is on the study, the protocol has been followed accurately, and there are no unreported medical misadventures.

5. Any unanticipated major adverse reactions or other medical misadventures must be reported immediately to the department chairperson, the Chief of the Medical Staff, the Clinical Investigations Coordinator and ultimately the commander IAW AFI 40-402. Such events will also need to be summarized in the subsequent progress report.

6. Please be advised that failure to provide proper consent forms, timely comprehensive progress reports, or adequate information on misadventures may lead to suspension of your protocol.

7. If you anticipate separating from the Air Force or changing assignments before the protocol is completed, you must notify the Clinical Investigations office as soon as this is known. You will be required to either formally close the protocol, or to have another investigator take over the study. The later process requires nomination by the flight chief, submission of a curriculum vitae, and approval by the Institutional Review Board.

8. Please indorse below and return the original to Clinical Investigations. I hope that your study will prove to be a worthwhile experience for both you and your patients. Let us know if there is any way we can assist you.

DBachman

DEBBIE BACHMAN
Clinical Investigations Coordinator

1st IND

TO: 74 MDOS/SGOA (Clinical Investigations)

I will need _____ informed consent document packages to begin my study.

Remarks by investigator:

Noted/Acknowledged

_____ _____

Principal Investigator Date

APPENDIX 2

IRB FORMS

- **USUHS FORM - 3202**

- **USUHS FORM - 3204**

USUHS FORM 3202
STUDENT and RESIDENT PHYSICIAN RESEARCH PROTOCOL

Protocol No.: _____

Student/Resident Investigator: Capt Mary Jo Burleigh, Capt Ronald Wyatt, and Capt Toney Banks

Department: Graduate School of Nursing – Nurse Anesthesia **Phone:** 937- 257-0596

Project Title: The Effect of IV Fentanyl on the Bispectral Index (BIS) Value and Recall

Research Advisor: Dr. Eugene Levine, Maj. William J. Craig **Department:** Nurse Anesthesia

	Graduate Ph.D. Student	year 1 or 2 of project (Circle one)
X	Nursing Masters Student	year 1 or 2 of project (Circle one)
	Medical Student	
	Master or Doctorate of Public Health Student	
	Physician Assigned for Graduate Medical Education Project Award (billeted resident physician)	

_____ Percent Effort for this project

1. Is this research project related to the advisor's active research project? _X_ Yes __ No
   If yes, enter the following information about the advisor's project.

   Protocol Number: **FWP20010043H**

   Project Title: **The Effect of IV Fentanyl on the Bispectral Index (BIS) Value and Recall**

   USUHS Department: Graduate School of Nursing – Nurse Anesthesia

2. USUHS Assurance Committees - Identify any relationship of this project with the sponsoring advisor's research protocol.

   A. If human subjects are involved (including human cell lines, human tissues or fluids, surveys, databases or medical records containing information about humans), circle (1) or (2) below:

      (1) The proposed protocol is specifically covered in all relevant details by the preexisting IRB approvals of the advisor's protocol and therefore, requires no additional approvals. Attach a copy of the USUHS approval letter and, if appropriate, a copy of the approved informed consent.

      (Covered in existing IRB approval at Wright-Patterson Medical Center)

      (2) The proposed protocol is not specifically covered in all relevant details by the preexisting approvals and a new completed Request for IRB Approval (USUHS Form 3204) is attached.

   B. If laboratory animals are involved, circle (1) or (2) below: N/A

      (1) The proposed protocol is specifically covered by the preexisting LARB approvals of the advisor's protocol and therefore, requires no additional approvals. Attach a copy of the USUHS LARB approval letter.

      (2) The proposed protocol is not specifically covered by the preexisting approvals and will require an addendum of the existing LARB approval or a new approval. Attach a new completed USUHS Form 3206. N/A

C. The use of biohazards, controlled or dangerous materials is covered as a supervised user by the existing BCD approval. If **yes**, submit user's and supervisor's names. **Otherwise**, attach a new completed USUHS Form 3207 N/A _ Yes

D. The student/resident uses radiation or radioactive material as a supervised user. If **yes**, attach the user's and supervisor's names. **Otherwise**, attach a new completed USUHS Form 3205. N/A _ Yes

3. BUDGET: (see USUHS Instruction 3200 for budget limitations)
Animals and Per Diem (Specify)

Supplies

Small Equipment (less than $1,000 per item) 250.00

Other (Specify):
(May not include non-mission essential travel or secretarial/administrative support)

Total: $ 250.00

3. SUMMARY OF RESEARCH PLAN: (Attach thesis proposal or summary. The research summary should include background, hypothesis, methodology and data analysis to be used; limit to 2 pages; 12 point font)

4. **The following signatures attest to the validity of the above information:**

	Typed Name	Signature	Date
Student/Resident Investigator:	**Capt Mary Jo Burleigh**		18 Jan 02
	Capt Ronald Wyatt		1-18-02
	Capt Toney Banks		1-13-02
Research Advisor:	Dr. Eugene Levine		6-18-02

5. Other Approvals:

Department Chair:

If: Graduate Student
Associate Dean for Graduate Education:
Cinda J. Heike, Ph.D.

Nursing Student
Dean, Graduate School of Nursing:
~~Patricia Hinton~~ Walker, PhD, RN, FAAN

Medical Student
Associate Dean for Student Affairs:
Richard M. MacDonald, M.D.

Dean, School of Medicine:
Val G. Hemming, M.D.

Physician Assigned for Graduate Medical Education
Associate Dean for Graduate Medical Education:
Howard E. Fauver, Jr., M.D.

6. In light of the above signatures, the project is approved for intramural funding.

Vice President for Research: **Steven G. Kaminsky, Ph.D.** _____

REA Date Stamp

USUHS FORM 3204
RESEARCH INVOLVING HUMAN SUBJECTS
(new or modification/addendum)

Protocol No.: _____

Principal Investigator: Capt Mary Jo Burleigh, Capt Ronald Wyatt, and Capt Toney Banks

Department: Graduate School of Nursing- Nurse Anesthesia **Phone** 937- 257- 0596

E-Mail: William.Craig@wpafb.af.mil **Pager or Other Phone Number** 937- 257- 0151

Project Title: The Effect of IV Fentanyl on the Bispectral Index (BIS) Value and Recall

PLEASE PROVIDE RESPONSES TO THE FOLLOWING:

1. ___x___ New protocol or ____ Modification/Addendum

2. Indicate the pages of proposal specifically applicable to the involvement or enrollment of volunteers, private information, or human-derived products.
   Pages: ____29 - 30_____

3. Check procedure(s) to be used:
   _____ Use of genetic testing or DNA analysis.
   _____ Use of blood or blood products: ( ) Blood Draw ( ) Blood Bank ( ) Other
   _____ Use of human tissue and/or bodily fluids including excreta and external secretions (sweat, saliva, amniotic fluid at the time of rupture of membrane).
   _____ Hair and/or nail clippings.
   _____ Teeth and/or dental material including plaque and calculus.
   _____ Prospective collection and use of donated, pathological and/or diagnostic specimens. **(Refer to question 15)**
   _____ Use of existing pathological and/or diagnostic specimens.
   - From where are these specimens being obtained?
   - Can the subjects from whom these specimens were obtained be identified directly or by the use of encoded identifiers?
     ( ) Yes ( ) No **(Refer to question 15)**

   _____ Use of human cell lines: ( ) Primary ( ) Immortalized
   _____ Moderate exercise by healthy volunteers.
   __X___ Recording of data using noninvasive procedures used in clinical practice.
   - Identify Bispectral Index (BIS) Value.

   _____ Study of existing data, documents, and/or records.
   - From where are these data being obtained?
   - Can the subjects from whom these data were obtained be identified directly or by the use of encoded identifiers?
     ( ) Yes (X) No

_____ Survey, interview, or educational (cognitive, diagnostic, aptitude, achievement) test or procedures or observation of public behavior.

- Can the subjects be identified directly or by identifiers?
  ( ) Yes (X) No
- Do the data collected involve sensitive information (e.g., drug and alcohol use, sexual practices, child or spousal abuse, or other information that could be criminal or damaging to one's financial or social standing, employability, insurability, or psychological well-being)?
  ( ) Yes (X) No

_____ Use of normal educational practices in accepted educational settings such as instructional strategies, effectiveness of or comparison among instructional techniques, curricula or classroom management methods.

_____ Use of taste and food quality evaluation and consumer acceptance studies?

4. Indicate the age and sex as well as the physical and psychiatric condition of the volunteers to be enrolled.
   Age: > 18 years of age
   Gender: Male and Female (non pregnant)
   Physical & psychiatric condition:
   Only patients with dementia or known allergy to fentanyl will be excluded.
5. Indicate the total number and rate of enrollment of volunteers.
   Total number: Twenty-five subjects will initially be enrolled in phase one, after which the data will be reviewed to determine if additional subjects should be enrolled and whether the study should be more targeted to a certain area. This data will then be presented to the IRB at the medical treatment facility. If it is determined that additional subjects should be enrolled to improve the significance of the study, the study should be redirected to a certain area, or changes should be made to the study methodology, this information will be incorporated into phase two of the data collection. (entire project)

   Rate: convenience sample The estimated time required for data collection for phase one is approximately two months. (#/ time period)

6. If applicable, explain with a compelling rationale the exclusion or under representation of one gender and/or minorities from the subject population. Pediatric and pregnant patients are excluded from the data collection due to the fact that this population is more difficult to obtain adequate numbers for participation in the study. Furthermore, they would not add any validity to the study.

7. Explain the inclusion of any vulnerable population (e.g., children, pregnant women, prisoners, cognitively impaired persons) and why that population is being studied. N/A

8. State how physical and psychiatric condition will be determined and by whom. Patients will be cleared by the primary surgeon and the staff anesthesiologist or anesthetist.

A. If normal volunteers are to be enrolled, state how this will be determined.

B. Describe the status of the volunteers relative to the principal investigator and/or USUHS (e.g., patient at Walter Reed, active duty, students, civilian employees, etc.) Active duty, retires, and dependents undergoing elective surgical procedures requiring general anesthesia.

11. Describe the status of the volunteer's Attending Physician to the project including his or her role in safeguarding the rights of the volunteer. The patient will only be permitted to participate in this study with the prior approval of his/her attending physician.

12. Identify the specific procedures, issues, and/or experimental drug administration involving the volunteers that are important for the IRB to consider. Describe possible risks, ethical issues, and/or side effects for each. Factors to consider including, but are not limited to, the following:

A. What is the volunteer being asked to do which they would not be doing unless part of this research project?

The patients will not be exposed to any additional risk by participating in this study. The patient's anesthetic plan will not be modified by participating in this study. The patient may feel less pain during there procedure but there is no other benefit to participating in this study except the knowledge that the patient is helping to improve medical knowledge. Risk associated with this study are no greater than those associated with general anesthesia.

There is an increased risk of nausea, vomiting, and itching which is a side effect of fentanyl. Other side effects which will be monitored include: slow breathing and heart rate, decreased blood pressure, decreased oxygen level, and allergic reaction.

B. Does the research collect personally sensitive information (e.g., drug and alcohol use, sexual practices, child abuse)? If so, how is confidentially protected? No

C. Does the research involve deception of the subject? If so, how is the subject debriefed after completion of the project? No

13. If this study involves the administration of drugs not approved by the FDA, state how approval will be obtained. N/A

14. Do any of the investigators have an equity or consultative relationship with a non-USUHS source related to this protocol which might be considered to be a conflict of interest? (If yes, please include a statement of disclosure.) No

15. Unless otherwise contained in your protocol, if using prospectively tissue, or any tissue linked to subject/patient identifiers:

A. How, where, and for how long will tissue/samples be stored?

B. Will patient data that can or will be linked to the tissue/samples be collected?

C. Will linkage to subjects be maintained or will samples be delinked?

D. Will any tissue/samples be left over at the end of the study and if so, what will be done with the tissue/samples?

13. Describe fully the modification(s) to your existing protocol to include rationale, procedures, numbers of subjects, etc. (Use blank pages if additional space is required.)

Twenty-five subjects will initially be enrolled in phase one, after which the data will be reviewed to determine if additional subjects should be enrolled and whether the study should be more targeted to a certain area. This data will then be presented to the IRB at the medical treatment facility. If it is determined that additional subjects should be enrolled to improve the significance of the study, the study should be redirected to a certain area, or changes should be made to the study methodology, this information will be incorporated into phase two of the data collection.

Phase one is projected to begin in August 2001 after obtaining approval by the Surgeon General's Research Oversight Committee (SGROC). The estimated time required for data collection for phase one is approximately two months. If it is determined to continue with phase two, data collection should be completed by the end of January 2002.

I have read and will comply with USUHS Instruction 3201, *"The Use of Human Volunteers in Research at the Uniformed Services University of the Health Sciences,"* March 1999.

I have read, understood, and will comply with the tenets contained in the Belmont Report ("Ethical Principles and Guidelines for the Protection of Human Subjects of Research," The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979. URL: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm).

Principal Investigator (signature)	**Date** 18 Jan 02
Principal Investigator (signature)	**Date** 18 Jan 02
Principal Investigator (signature)	**Date** 18 Jan 02
Associate Investigator	**Date** 18 Jan 02

APPENDIX 3

Appendix 11.0

SCHOLARLY PROJECT APPROVAL FORM

TITLE OF PROJECT

THE EFFECT OF IV FENTANYL ON BIS VALUE AND RECALL

Capt Mary Jo Burleigh
Capt Ronald Wyatt

APPROVED:

Eugene Levens 23 April 2001
Chair Date

Lisa Petty 23 APR 01
Member Date

William John Craig 23 Apr 01
Member Date

Member Date

APPROVED:

Faye G. Abdellah May 8, 2001
Faye G. Abdellah, EdD, ScD, RN, FAAN Date
Dean

APPENDIX 4

INFORMED CONSENT DOCUMENT

Wright-Patterson Air Force Base Medical Center

Fairborn, OH

(Base AFB, State, ZIP)

(IRB Approval Dates 1 Aug 01 - 1 May 02)

PRIVACY ISSUES: Records of my participation in this study may only be disclosed in accordance with federal law, including the including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations. I have read the Privacy Act Statement contained in DD Form 2005. I understand that records of this study may be inspected by the U.S. Food and Drug Administration (FDA), the sponsoring agency and/or their designee, if applicable.

TITLE OF STUDY

"The effect of IV Fentanyl on BIS Value and Recall"

INVESTIGATORS' NAMES, DEPARTMENTS, PHONE NUMBERS

Capt Mary Jo Burleigh, Nurse Anesthesia Residency Program

Capt Ronald Wyatt, Nurse Anesthesia Residency Program

PURPOSE OF STUDY

You are asked to consider participation in a research study at Wright Patterson Air Force Base Medical Center, Dayton, OH, entitled ***"The Effect Of IV Fentanyl of BIS Value and Recall".***

This study will enroll 75 of subjects over a period of two months. You will be asked to make no additional outpatient visits during your participation.

PROCEDURES

If you volunteer to participate in this study, we will ask you to do undergo the following procedures:

1. An intravenous (IV) insertion, which is necessary to give the fentanyl through. Insertion of an IV is a normal part of surgery and you will not be asked to undergo any other needle sticks or blood draws for this study.
2. Application of a small adhesive electrode to your forehead to monitor your brain waves while the fentanyl is being given.
3. Administration of a small to moderate dosage of fentanyl depending on your response to it. This is normally used as a pain medication (like morphine) but it can make people feel sedated as well. Fentanyl is normally given before and during surgery to ease pain and to relax you.
4. You will be shown a picture when you are sedated and we will ask you to try and recall that picture once you have recovered from your surgery; if we are unable to do this before you leave the hospital, we will call you to see if you can describe the picture to us.

RISKS/INCONVENIENCES

There are no additional risks associated with this study than would normally be associated with surgery and anesthesia.

The drug used in this study is Fentanyl, also known as Sublimaze. Possible side effects of this drug are itching, nausea, and vomiting; all of which are treatable. Side effects you will be monitored for include: slow breathing and heart rate, decreased blood pressure, decreased oxygen level, and allergic reaction.

If you are pregnant or breast feeding, you are ineligible for this study. If it is possible that you may be pregnant, a pregnancy test will be done.

BENEFITS

The possible benefit of your participation is a state of relaxation from the IV fentanyl given before surgery so you may have decreased anxiety before going into the operating room.

ALTERNATIVES

If you decide not to participate in this study, other treatment, including no sedation and/or administration of other sedatives ad determined by your anesthesia provider may be available to you.

EVENT OF INJURY

Your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if you have questions about your rights or if you believe you have received a research-related injury, you may contact the Director of the Clinical Investigation Facility (or locally determined POC) at ***(phone number)***, the Customer Subject Representative at ***(phone number)***, the medical monitor or the investigator.

OCCURRENCE OF UNANTICIPATED ADVERSE EVENT

If an unanticipated event occurs during your participation in this study, you will be informed immediately. If you are not competent at the time to understand the nature of the event, such information will be brought to the attention of your next of kin.

CONFIDENTIALITY

When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. All of the records will be stored for a period of five years by the research department; again, no identifying information will maintained with your record. Complete confidentiality cannot be promised, particularly for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities.

DECISION TO PARTICIPATE

The decision to participate in this study is completely voluntary on your part. You may choose not to take part in the study. Capt Mary Jo Burleigh or Capt Ronald Wyatt will answer any questions you have about this study, your participation, and the procedures involved.

You may withdraw your consent at any time. Your decision will not affect your surgical or anesthetic care in any way. If you decide to discontinue further participation in this study, you will continue to receive acceptable standard medical treatment. The investigator or anesthesia provider may terminate your participation in this study at any time if he/she feels this to be in your best interest.

I have read all of the above. My questions have been answered concerning areas I did not understand. I am willing to take part in this study. After I sign this form, I will receive a copy.

_____ _____

(Subject's Printed Name) (Subject's SSN)

_____ (___)_____ _____

*(Subject's Signature) (FMP & Sponsor's SSN) (Date & Time)

_____ _____

(Advising Investigator's Signature) Date

_____ _____

(Witness's Signature) Date

APPENDIX 5

Frequencies

Statistics

		subject age	UGKG
N	Valid	20	20
	Missing	0	0
Mean		43.60	2.6947
Median		42.50	2.3250
Mode		31[a]	2.50[a]
Std. Deviation		13.76	1.4684
Variance		189.41	2.1562
Range		48	6.03
Minimum		21	1.11
Maximum		69	7.14

a. Multiple modes exist. The smallest value is shown

Frequency Table

subject age

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	21	1	5.0	5.0	5.0
	24	1	5.0	5.0	10.0
	25	1	5.0	5.0	15.0
	31	2	10.0	10.0	25.0
	35	2	10.0	10.0	35.0
	39	1	5.0	5.0	40.0
	40	2	10.0	10.0	50.0
	45	1	5.0	5.0	55.0
	46	1	5.0	5.0	60.0
	48	1	5.0	5.0	65.0
	54	2	10.0	10.0	75.0
	56	1	5.0	5.0	80.0
	57	1	5.0	5.0	85.0
	58	1	5.0	5.0	90.0
	64	1	5.0	5.0	95.0
	69	1	5.0	5.0	100.0
	Total	20	100.0	100.0	

UGKG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.11	1	5.0	5.0	5.0
	1.15	1	5.0	5.0	10.0
	1.23	1	5.0	5.0	15.0
	1.32	1	5.0	5.0	20.0
	1.64	1	5.0	5.0	25.0
	2.00	1	5.0	5.0	30.0
	2.10	1	5.0	5.0	35.0
	2.17	1	5.0	5.0	40.0
	2.22	1	5.0	5.0	45.0
	2.25	1	5.0	5.0	50.0
	2.40	1	5.0	5.0	55.0
	2.50	2	10.0	10.0	65.0
	2.63	1	5.0	5.0	70.0
	3.13	2	10.0	10.0	80.0
	4.17	1	5.0	5.0	85.0
	4.54	1	5.0	5.0	90.0
	4.57	1	5.0	5.0	95.0
	7.14	1	5.0	5.0	100.0
	Total	20	100.0	100.0	

Correlations

Correlations

		UGKG	lowest BIS
UGKG	Pearson Correlation	1.000	-.086
	Sig. (2-tailed)	.	.720
	N	20	20
lowest BIS	Pearson Correlation	-.086	1.000
	Sig. (2-tailed)	.720	.
	N	20	20

APPENDIX 6